

Comparison of efficacy of Natural honey and Triamcinolone acetonide (0.1%) in the healing of oral ulcers—A clinical study

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ABSTRACT

Background: To compare the effectiveness of Natural Honey with Triamcinolone acetone- ide (0.1%) on the healing of Oral ulcers.

Methods : Seventy four oral ulcers (forty nine recurrent aphthous stomatitis , sixteen aphthous like ulcers in Oral submucous fibrosis and nine traumatic ulcers) were evalu- ated and each half of them were advised to apply honey and triamcinolone acetonide. Pain score (visual analog scale), ulcer size (measured by William’s Periodontal Probe), erythema level was evaluated on first day and after drug application . Statistical Analysis was done and tabulated by using SPSS software.

Results: Natural honey showed significant reduction in pain score and ulcer size ($p < 0.05$) as compared to triamcinolone acetonide on third day. There was similar reduction in erythema level ($p < 0.05$) in both groups. Natural honey showed significant reduction in moderating pain in recurrent aphthous stomatitis and aphthous like ulcers in oral sub- mucous fibrosis where as insignificant reduction in ulcer size and erythema level in all the three subgroups. Also, Triamcinolone acetonide showed insignificant reduction in moderating pain, ulcer size and erythema level in all the subgroups of oral ulcers. **Conclusion:** The data clearly demonstrate that with the use of honey, no allergic reac- tion elicited and no significant side effects were reported. In addition to its valuable nutritional constituents, honey has anti-inflammatory, antioxidant activities that make it a suitable natural subject for healing oral ulcers. Thus, it might help clinicians to give alternative treatment of oral ulcers for their patients since honey is worldwide available and cheaper readily available across the globe.

ARTICLE HISTORY

Received March 4, 2017

Accepted November 16, 2017

Published December 19, 2017

KEYWORDS

Natural Honey;
Triamcinolone acetonide;
Recurrent Aphthous
Stomatitis, Traumatic Ulcer;
Aphthous like Ulcers in Oral
submucous fibrosis

Introduction

Oral ulceration is a common complaint of patients attending out-patient departments [1] Recurrent aphthous ulceration or recurrent aphthous stomatitis (RAS) is the most common oral mucosal disease known to human beings. The term “aphthous” is derived from a Greek word “aphthae” which means ulceration [2].

Aphthous Stomatitis affects 10–20% of the ulcer population. The incidence in both sexes are almost equally affected with a slightly higher incidence in females than males [3]. The clinical manifestations range from mild ulceration that heals within a few

days to deep and painful ulcers that persist for as longer time [4].

Recurrent aphthous stomatitis or recurrent aphthous ulcers, frequently referred as canker sores, is a chronic, incurable condition can be painful for the patient, making them uncomfortable to speak, eat, drink or swallow [5].

RAU is characterized by the periodic appearance of the painful small crateri-form ulceration on the mucosa of oral cavity i.e. vestibule, cheeks, lips, tongue, palate, floor of the mouth and pharynx. It has a bright red circular inflammatory zone with a pseudomembrane ranging from gray to yellow in color [6].

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It has a higher prevalence in younger adults and the incidence and severity would decrease with age [7]. Epidemiologic studies have proven that the prevalence of RAS is influenced by the population studied, use of diagnostic criteria, and environmental factors present [8]. The etiology of RAS lesions is unknown, but there are many local, systemic, immunologic, nutritional, and microbial factors which have been proposed as causative agents [5,7,9,10]. Trauma to the oral mucosa due to local anesthetic injections, sharp tooth, dental treatments, and tooth brush injury may predispose to the development of Traumatic ulceration [1].

There are many conditions of the oral cavity that manifest as ulcerations, common lesions include Herpetic gingivostomatitis, Pemphigus, Oral submucous fibrosis.

Oral submucous fibrosis is a chronic condition of the oral cavity that presents as erythematous lesion in conjunction with petechiae and vesicles. The vesicles with time break to form ulcers with marked erythema [11].

The management of oral ulcers has been as varied due to its proposed etiologies. Mostly treatments are directed primarily toward the symptomatic management. Therefore, it is necessary to reduce the inflammation of the ulcers and relieve the pain of the patients by using systemic or topical agents. The primary goals of therapy should be relief of pain, reduction of ulcer duration, and restoration of normal oral function. The secondary goals include reduction in frequency and severity of recurrences and maintenance of remission.

Topical treatments that are commonly used include topical glucocorticoids, antibiotics, local analgesics and laser therapy. Palliative approach (e.g. Topical agents: home remedies, prescribed analgesics), anti-inflammatory and antimicrobial agents (e.g. Topical such as creams, ointments, gels, rinses); intralesional (perilesional) corticosteroid injections, and systemic corticosteroids or combined therapy.

Natural Honey has been described and explained in ancient and modern medicine as being effective in the healing of various infected wounds, there have been few reports of its use in the healing of burns, ulcers and open wounds [3,6,12,13].

The use of natural honey as a traditional medicine for microbial infections dates back to ancient times [14].

Although not an herb, honey is a plant by-product and used medicinally around the world. It is an anti-bacterial, anti-viral and anti-fungal, and all of these properties make it ideal for healing wounds. It also dries out wounds effectively because of its low water content while its high sugar content keeps microorganisms from growing [15].

There are certain physicochemical properties of natural honey of Vidarbha region (which was used): **Moisture** depends on the botanical origin of the sample, the degree of ripeness, Processing techniques and storage conditions. Moisture content in the sample of Vidarbha region ranges from 19.1–23.1. **Free acidity** of honey samples of Vidarbha region ranged from 15 to 47 respectively, high free acidity values may indicate the fermentation of honey sugar by yeasts. **Sugars** - Honey consists of mostly glucose and fructose. The actual proportion of fructose to Glucose depends largely on the source of the nectar. Honey with high fructose to glucose ratios would remain liquid for longer periods and less prone for granulation [16].

In view of the multiple and varied agents that have been implied to treat oral ulcers, it would seem appropriate to use the least toxic and most feasible agent that can provide symptomatic relief and hence the current management protocol is aimed towards ameliorating the symptoms. In order to clinically determine the efficacy of Honey in shortening the clinical course of oral ulcers, a comparative study was conducted versus Triamcinolone Acetonide 0.1% in orabase (the widely used topical corticosteroid agent) to determine the control of symptoms associated with oral ulcers through a prospective, clinical trial.

Materials and Methods

The present prospective study was conducted in the Department of Oral Medicine and Radiology, Sharad Pawar Dental College and Hospital DMIMS (DU), Wardha, after taking approval from the **Institutional Ethics Committee**, during the period October 2014–March 2016. The subjects were informed in detail about the study and after obtaining an informed consent, the patients were examined thoroughly and detailed case history was recorded.

This prospective study consisted of 74 patients selected from amongst the patients visited at the outpatient department confirming the presence of oral ulcers. The subjects were divided into two equal groups for the study:-

GROUP A: 37 Patients treated with Natural Honey.

GROUP B: 37 Patients treated with Triamcinolone Acetonide 0.1%.

Inclusion Criteria

- Males and females aged from 15–60 years old.
- Patient with single or multiple ulcers with size less than 50mm in diameter and duration less than 72 hours. Patients with multiple ulcers, only one ulcer that occurred most recently in an area easily accessible.
- Patients with local oral factors that could favor the appearance of aphthae (traumatic injury, inadequate dental prosthesis etc.).
- Patients with Oral Submucous Fibrosis associated ulcers.

Exclusion Criteria

- Patients with history of previous local treatment within 48 hours of ulceration.
- Subjects suffering from major systemic disorders (crohn’s disease, behcets disease, anemia).
- Patients with known history of serious drug hypersensitivities.

To measure pain, a Wong Baker Face Scale/visual analog scale (VAS) consisting of a 10 cm horizontal line between poles connoting no pain to unbearable pain was used. The subjects were asked to mark the line with a vertical line at the point that best represented the pain level of the ulcer on first day of visit and third day.

Ulcer Size Measurement

The maximum diameter of the ulcer was assessed with a William’s calibrated Periodontal Probe on day 1 and on treatment day 3. Maximum diameter was evaluated as length and breadth of ulcer which is further multiplied to calculate the Area of Ulcer [Figures 1–4].

Erythema Level Measurement

Degree of erythema was evaluated on a four point scale ranging from 0 to 3 based upon the methods of [Bhat S Suraksha D⁹] Erythema level was measured on the 1st day and third day [Figures 1–6].

CRITERIA	ERYTHEMA
0	No Erythema
1	Light red/pink
2	Red but not dark in colour
3	Very red/dark in colour



Figure 1. Pre-treatment view of oral ulcer in honey group. Ulcer measured for Area by William’s periodontal probe.



Figure 2. Post-treatment view of oral ulcer in honey group. Ulcer completely diminished after 3rd day treatment.

Traumatic Ulcer

The offending agent (sharp cusp, rough prosthesis) was eliminated on the first day before drug application.

Preparation of Drugs

- Natural honey was collected, processed and packed from **National Centre for Bee Development, Wardha**. Bees collecting natural honey were of Genus **Apis Dorsati** (wild bees) of Vidarbha Region. Bees nest their hives over the plant of **Neem, Dehada, Behada** which yield yellow flower (more pollen grains) Ratio of Glucose/Fructose is above 1% which shows the less property of granulation and further coagulation. Honey collected for study was collected in Rainy season (property – less moisture and less infectivity) (15) Natural honey was tested in Dish Diffusion Table for its viscosity and moisture

level. 10gm natural honey was then measured through a pipette and packed in sealed collapsible plastic container.

- Triamcinolone acetonide 0.1% was taken from **Oraways, Mankind Pharmaceutiucal Limited; New Delhi**. 10gm tubes were prepared and purchased, especially for mouth ulcers. The agent was taken in orabase vehicle.

Natural honey and Triaminoclone acetoniide 0.1% was provided and method of application was explained to all the subjects. Subjects were re-examined after three days. Efficacy indices were calculated for all the subjects.



Figure 3. Pre-treatment view of oral ulcer in Triamcinolone group. Ulcer measured for Area by William’s periodontal probe.

Efficacy Index

The efficacy indices (EI) of the ulcer size and pain improvement, erythema level were calculated with the following formula (V3 refer to the values measured at day 3 visit, while V1 refers to the baseline value measured before the study entry):

$$EI = \frac{[V3-V1]}{V1} \times 100\%$$

The EI were evaluated on a 4-rank scale:

- Heal: EI = 100%
- Marked improvement: $100\% > EI \geq 70\%$
- Moderate improvement: $70\% > EI \geq 30\%$
- No improvement: $EI < 30\%$

Safety Evaluation

Subjects were specifically questioned about adverse events at each visit and was recorded in the case report forms.



Figure 4. Post-treatment view of oral ulcer in Triamcinolone group. Ulcer showing reduction in erythema level and size of ulcer.

Statistical Methods Employed

Data was tabulated for statistical analysis. The software used in the analysis were SPSS 17.0 and Graph Pad Prism 5.0 version and $p < 0.05$ is considered as level of significance. student t test and chi square test was done to obtained to the values.

Observations and Results

A total of 74 patients were selected from the dental OPD in the department of OMR with age ranging from 15 to 60 years. They were divided into two groups, Group A (NH) and Group B (TA) in which the mean age in group A was found to be 29.05 ± 12.46 years whereas Group B was found to be 27.70 ± 10.40 years. There were 15 (40.54%) males and 22 (59.46%) females in group A and 12 (32.43%) males and 25 (67.57%) females in group B.

Efficacy Index

Pain Score

The mean pain score on first day in honey group was 4.81 ± 2.06 and in triamcinolone group was 5.13 ± 1.66 whereas, on third day in honey group was 1.43 ± 1.81 and in triamcinolone was 2.75 ± 1.16 indicating statistically significant difference (Table 1). There was more pain reduction in honey group as compared with the triamcinolone group. There was more “heal” and “marked

improvement” grading in honey group and more “moderate improvement” grading in triamcinolone group (Table 2).

Table 1. Comparison of Efficacy Index for pain score ulcer size erythema level in two groups. Natural honey showed more efficacy in moderating pain and reducing ulcer size than Triamcinolone Acetonide. Both agents showed similar efficacy in reducing erythema level.

Parameter	Pain Score		Ulcer Size		Erythema level	
	NH	TA	NH	TA	NH	TA
Mean	69.69	47.68	78.42	45.40	57.50	65.29
Std. Deviation	47.85	18.21	32.40	20.73	45.22	37.56
t-value	2.61		5.22		0.83	
p-value	0.011 S, p<0.5		0.0001 S, p<0.05		0.40 NS, p>0.05	

Ulcer Size

The mean ulcer size on first day in honey group was 8.00 ± 8.80 and in triamcinolone acetonide group was 7.40 ± 5.05 whereas, on third day in honey group was 2.01 ± 4.49 and in triamcinolone was 4.02 ± 3.13 indicating statistically significant difference (Table 1). Natural honey group showed more reduction in ulcer size as compared to triamcinolone acetonide group. There was more “heal” grading in honey group and more “moderate improvement” grading in triamcinolone group (Table 2).

Table 2. Comparison of different grading’s of efficacy index pain score ulcer size erythema level in two groups of patients. Honey and triamcinolone acetonide group showed more “marked improvement” grade.

Grading	Honey Group	Triamcinolone Group	χ2-value
Heal	16 (43.2%)	2 (5.4%)	30.57 P = 0.0001,S
Marked Improvement	7 (18.9%)	0 (0%)	
Moderate Improvement	12 (32.4%)	30 (81.10%)	
No Improvement	2 (6.4%)	5 (13.5%)	

Heal-1; Marked Improvement-2; Moderate Improvement-3; No Improvement-4.

Erythema Level

The mean erythema level on first day in honey group was 1.32 ± 0.57 and in triamcinolone group was 1.97 ± 0.72 whereas, on third day in honey group was 0.62 ± 0.68 and in triamcinolone was 0.72 ± 0.83 showing statistically insignificant difference in both groups. NH and TA showed similar reduction in erythema level. (Table 1). There was more “heal” grading and more “moderate improvement” grading in triamcinolone group (Table 2).

Efficacy Index Between Subgroups

Honey Group

In Honey group, the mean pain score on first day in OSMF-U subgroup was 4.66 ± 1.96, RAS subgroup was 4.75 ± 2.10, TU subgroup was 5.66 ± 2.51 whereas, on third day in OSMF-U subgroup was 0.83 ± 0.98, RAS subgroup was 1.17 ± 1.41, TU subgroup was 5.00 ± 3.00. In Honey group, mean pain score was more reduced in OSMF-U AND RAS subgroup as compared to TU.

In Honey group, the mean ulcer size on first day in OSMF-U subgroup was 5.00 ± 3.22, RAS subgroup was 8.83 ± 9.70, TU subgroup was 6.33 ± 7.50 whereas, on third day in OSMF-U subgroup was 0.75 ± 1.17, RAS subgroup was 2.25 ± 5.04, TU subgroup was 2.33 ± 3.21. The mean ulcer size was similarly reduced in OSMF-U, RAS and TU subgroup.

In Honey group, the mean erythema level on first day in OSMF-U subgroup was 1.66 ± 0.81, RAS subgroup was 1.28 ± 0.53, TU subgroup was 1.00 ± 0.00, whereas on third day in OSMF-U subgroup was 1.00 ± 0.89, RAS subgroup was 0.53 ± 0.63, TU subgroup was 0.66 ± 0.57. In Honey group, mean erythema level was similarly reduced in OSMF-U, RAS and TU subgroup. (Table 3).

Triamcinolone Group

In triamcinolone group, the mean pain score on first day in OSMF-U subgroup was 5.66 ± 2.94, RAS subgroup was 5.03 ± 1.42, TU subgroup was 5.00 ± 0.00, whereas the mean pain score on third day in OSMF-U subgroup was 3.33 ± 0.81, RAS subgroup was 2.75 ± 1.14, TU subgroup was 1.66 ± 1.52. on applying efficacy index, mean pain score was similar in OSMF-U, TU and RAS subgroup.

In triamcinolone group, the mean ulcer size on first day in OSMF-U subgroup was 5.00 ± 3.79, RAS subgroup was 7.92 ± 5.42, TU subgroup was 7.33 ± 2.30. however, the mean pain score on third day in OSMF-U subgroup was 5.83 ± 6.24, RAS subgroup

was 3.32 ± 1.84 , TU subgroup was 7.00 ± 1.73 . On evaluation, it was similar in OSMF-U, TU AND RAS subgroup.

In triamcinolone group, the mean erythema level on first day in OSMF-U subgroup was 1.83 ± 0.75 , RAS subgroup was 2.00 ± 0.76 , TU subgroup was 2.00 ± 0.00 , whereas the mean pain score on 3rd day in OSMF-U subgroup was 0.83 ± 0.98 , RAS subgroup was 0.67 ± 0.81 , TU subgroup was 1.00 ± 1.00 . The

mean erythema level was similar in OSMF-U, TU AND RAS subgroup on first & third day (Table 4).

For gradings, RAS subgroup revealed maximum "heal" grading and TU, OSMF-U subgroup revealed more "moderate improvement" grade in efficacy index in pain score, ulcer size, erythema level for honey and triamcinolone acetamide treated patients (Table 2).

Table 3. Comparison of efficacy index for pain score ulcer size erythema level in natural honey group between subgroups of oral ulcers. Natural honey has more efficacy in modulating pain in recurrent aphthous stomatitis and aphthous like ulcers in oral submucous fibrosis than traumatic ulcers. All the three subgroups showed nearly similar reduction in ulcer size and erythema level.

Parameter	Pain Score			Ulcer size			Erythema Level		
	OSMF-U		RAS	OSMF-U		RAS	OSMF-U		RAS
	RAS	TU	TU	RAS	TU	TU	RAS	TU	TU
Mean Difference	-2.52	7.08	9.61	-3.25	95.83	99.09	-24.80	5.55	30.35
p-value	0.984, NS	0.951, NS	0.883, NS	0.983, NS	0.005, S	0.001, S	0.446, NS	0.983, NS	0.514, NS

Table 4. Comparison of efficacy index for pain score ulcer size erythema level in triamcinolone acetamide group between the subgroups of oral ulcers. All the three subgroups showed nearly similar reduction in pain score ulcer size and erythema level from triamcinolone acetamide drug treatment.

Parameter	Pain Score			Ulcer size			Erythema Level		
	OSMF-U		RAS	OSMF-U		RAS	OSMF-U		RAS
	RAS	TU	TU	RAS	TU	TU	RAS	TU	TU
Mean Difference	-8.16	-27.38	-19.21	5.75	11.23	5.47	-3.35	13.88	17.23
p-value	0.559, NS	0.084, NS	0.183, NS	0.818, NS	0.735, NS	0.905, NS	0.979, NS	0.866, NS	0.742, NS

Discussion

The oral cavity plays an essential role in many key bodily functions, including mastication, digestion, swallowing, respiration, and communication. Ulceration of the oral mucosa may be due to trauma, recurrent aphthous stomatitis, microbial infections, mucocutaneous disease, systemic disorders and drug therapy (16). The best treatment that can be achieved is to avoid local traumatic precipitants, lessen the pain and duration of ulceration by suppressing the local immune response, and prevent secondary infection (11).

The primary aim of this paper was to show that a new formulation for topical application of natural honey would be effective in managing common oral mucous membrane diseases, namely recurrent aphthous stomatitis (RAS), oral submucous fibrosis associated ulcers and traumatic ulcers.

When honey group was compared with triamcinolone acetamide in terms of pain score, the present study showed statistically significant difference. The present clinical trial proved that the pain reduction was seen more in the natural honey group as compared to the triamcinolone acetamide group

on 3rd day. This finding was in accordance with El-Haddad et al. [11] who also reported better effectiveness of honey for pain relief than triamcinolone acetonide (Table 1).

In the present study, when use of natural honey was compared with triamcinolone acetonide with regards to ulcer size, it showed that honey has significant reduction in ulcer size on 3rd day as compared to 1st day (Table 1). This might be attributed to the healing effect of honey which is ascribed to its broad-spectrum antibacterial action, high acidity (with a pH between 3.2 and 4.5) that inhibits the growth of microorganisms, high sugar content, high viscosity, immunomodulatory action. The study was in accordance with El-Haddad SA et al. [11], Mohammed SS and Al-Douri AS [3], Gichki AS et al. [6].

When natural honey was compared with triamcinolone in terms of erythema level, there was statistically insignificant difference in both groups. (Table 1). Effectiveness of reducing erythema level in natural honey and triamcinolone acetonide was similar on third day whereas, El-Haddad SA et al. [11], observed and reported that the honey group was superior from both triamcinolone acetonide and Orabase groups in resolution of erythema and accelerating the ulcer healing process. Triamcinolone acetonide 0.1% is contraindicated in cases of intraoral bacterial or viral infection. When topically applied intraorally to large areas or under occlusive dressings, it can be absorbed in sufficient amounts to cause systemic effects. Whereas, Honey has excellent anti-inflammatory properties, as indicated in the present study, and many other clinical properties, including antibacterial and anti-*Candida* properties that hasten the healing process. So, it can be used as a better alternative for reducing the erythema level.

Honey and triamcinolone acetonide 0.1% were almost equally effective in reducing pain score, ulcer size, erythema level in RAS, OSMF-U, TU However, there is no studies documented in the literature till date, which limits the discussion of agents in relation to pain score, ulcer size erythema level (Tables 3-4).

Conclusion

With the use of honey, no allergic reaction is elicited and no significant side effects were reported. In addition to its valuable nutritional constituents, honey has anti-inflammatory and antioxidant activities, its broad spectrum antibacterial action, high acidity that inhibit microorganism, high sugar

content, high viscosity and immunomodulatory action makes it a suitable natural subject for healing oral ulcers. Thus, this finding might help clinicians to give alternative treatment of oral ulcers for their patients since honey is worldwide available and cheaper.

Conflict of Interest

There were no conflict of interest present.

Acknowledgement

Natural honey was obtained from the National Center for bee development. Nalwadi, Wardha.

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